REMARKS

Claims 1, 6, and 38 have been amended without any intention of disclaiming equivalents thereof, and claims 2-4 and 57-116 are canceled without prejudice to reintroducing claims directed to this subject matter in this or another patent application. Support for the amendments is found in the specification, for example, in Figures 1A-1D (the round structures are the basal lamina tubes; this is a cross-section of the entire processed nerve); on page 27, lines 16-23; and on page 55, lines 10-22. It is respectfully submitted that no new matter is added. Accordingly, after entry of this amendment, claims 1, 6-23, 30-40, 42-56, and 117-123 are pending.

Rejection Under 35 U.S.C. §112, Second Paragraph

Claims 1-4, 6-23, 30-40, 42-56, and 116-123 (and, specifically, claims 1, 38, and 116) presently stand rejected under 35 U.S.C. §112, second paragraph for being indefinite with regard to the term "predegenerating." Claims 2-4 and 116 are cancelled without prejudice, rendering their rejection moot. Additionally, without acquiescing to or necessarily agreeing with this rejection, claims 1 and 38 are amended to remove the term "predegenerating" in order to advance prosecution. Accordingly, Applicant respectfully traverses this rejection.

Claims 1-4, 6-23, 30-40, 42-56, and 116-123 (and, specifically, claims 1, 6, 38, and 116) presently stand rejected under 35 U.S.C. §112, second paragraph for being indefinite with respect to the recitation of "use." Claims 2-4 and 116 are cancelled without prejudice, rendering their rejection moot. Without acquiescing to or necessarily agreeing with this rejection, claims 1, 6, and 38, are amended without prejudice to remove the term "use" in order to advance prosecution. Accordingly, Applicant respectfully traverses this rejection.

Rejections Under 35 U.S.C. §102

The La Fleur Reference

Claims 1, 6-15, 17-21, 30-40, 42-51, 53-56, 116-120, 122, and 123 stand rejected over La Fleur *et al.* (1996), J. Exp. Med. 184: 2311-2326 ("La Fleur") under 35 U.S.C. §102(b). Claim 116 is cancelled without prejudice, rendering its rejection moot. La Fleur describes a study intended to identify major MMPs and TIMPs involved in repair after peripheral nerve injury and the possibility that protection of basement membrane (BM) from proteolytic degradation is a relevant mechanism during repair of injury to nerve. (Page 2312, left column.) La Fleur found

that, in response to a crush injury, TIMP-1 was induced. (Abstract.) TIMP-1 protected BM type IV collagen from degradation by exogenous MMP-9 in cryostat sections of nerve *in vitro*. (*Id.*) La Fleur concludes that TIMP-1 may protect BM from uncontrolled degradation after injury. (*Id.*) More specifically, La Fleur suggests that, *in vivo*, TIMP-1 protects specific BM components of injured nerve from degradation by MMPs. (Page 2322, left column.)

La Fleur simply does not teach degrading chondroitin sulfate proteoglycan (CSPG) of a nerve graft comprising a nerve tissue segment and having an intact basal lamina tube by *in vitro* culturing, thereby enhancing post-implantation axonal traversal of an interface between the nerve graft and host nerve tissue relative to an untreated nerve graft as recited in amended independent claim 1 and 38. In fact, La Fleur teaches essentially the opposite of the present invention. Whereas Applicant's claimed invention involves degradation of CSPG, La Fleur teaches that TIMP-1 preserves CSPGs by protecting against MMPs during *in vivo* degeneration (*i.e.*, Wallerian degeneration). The fact that La Fleur teaches that TIMP-1 protects basement membrane from degradation by MMPs (page 2322, left column), particularly during Wallerian degeneration to promote axonal regrowth *in vivo* (page 2323, right column), indicates that La Fleur's mechanism would not enhance post-implantation axonal traversal of an interface between the nerve graft and host nerve tissue as required by the present claims. Thus, not only does La Fleur fail to teach degradation of CSPG, but in fact — in preserving CSPGs through TIMP-1 rather than degrading CSPGs — teaches behavior diametrically opposed to that claimed herein.

For these reasons, amended independent claims 1 and 38 are novel over La Fleur. Claims 6-15, 17-21, 30-40, 42-51, 53-56, 117-120, 122, and 123, which depend directly or indirectly from an allowable base claim, also are allowable. Applicant respectfully requests that this rejection be reconsidered and withdrawn.

The Dennis Reference

Claims 1-4, 6-15, 17-21, 30-32, 34-40, 42-45, 47-51, 53-56, 116, 119, 122, and 123 stand rejected over U.S. Patent No. 6,448,076 to Dennis *et al.* ("Dennis") under 35 U.S.C. §102(e). Claims 2-4 and 116 are cancelled without prejudice, rendering their rejection moot. Dennis reports on a method of acellularization. Briefly, rat peripheral nerve segments are surgically removed, pinned at slack length within a culture dish, and immediately submersed in Dulbecco's Phosphate Buffered Saline (PBS). Then, the acellularization method is carried out at room

temperature. (Col. 3, lines 34-50.) These acellularized nerve grafts reportedly support axonal regeneration and allow end-organ reinnervation. (Col. 6, lines 21-24.)

For the reasons that follow, Applicant respectfully submits that the rejected claims are neither anticipated nor even suggested by Dennis. In particular, amended independent claims 1 and 38 recite, in part, degrading chondroitin sulfate proteoglycan (CSPG) of a nerve graft comprising a nerve tissue segment and having an intact basal lamina tube by *in vitro* culturing, thereby enhancing post-implantation axonal traversal of an interface between the nerve graft and host nerve tissue relative to an untreated nerve graft.

With regard to amended independent claims 1 and 38, Dennis does not describe a degrading step by *in vitro* culturing. In Dennis, the nerve is placed in PBS and then acellularization is carried out. There is no *in vitro* culturing.

Furthermore, with regard to amended independent claims 1 and 38, Dennis does not describe degrading CSPG of the nerve graft and enhancing post-implantation axonal traversal of an interface between the nerve graft and host nerve tissue. In fact, Dennis teaches just the opposite. Dennis states, "the acellularization method of the present invention...preserves the basal lamina in order to maintain the appropriate molecular signals and adhesion molecules to enhance axonal regeneration." (Dennis, col. 6, lines 7-12; emphasis added.) Thus, Dennis fails to teach degrading CSPG of a nerve graft.

Moreover, as explained in the present application, culturing conditions under certain circumstances activate CSPG-degrading enzymes (specification, page 27, lines 20-23) and/or involve addition of CSPG-degrading enzymes (specification, page 28, lines 18-20 and Example 3). These conditions enhance post-implantation axonal traversal of an interface between the nerve graft and host nerve tissue. Although Dennis does describe nerve grafts that support axonal regeneration, it does not follow that either degradation of CSPG or enhancement of post-implantation axonal traversal of an interface between the nerve graft and host nerve tissue are present. This is demonstrated, for example, by Applicant in Example 18. Example 18 and Figures 20A and B indicate that axonal regeneration into acellular nerve grafts is enhanced by *in vitro* predegeneration, but that axonal growth occurred within the basal lamina tubes in both the predegenerated and control conditions. Thus, it is improper to infer the presence of either

degradation of CSPG or enhancement of post-implantation axonal traversal of an interface between the nerve graft and host nerve tissue from a graft that supports axonal regeneration.

Accordingly, for the reasons provided above, amended independent claims 1 and 38 are novel over Dennis. Claims 6-15, 17-21, 30-32, 34-40, 42-45, 47-51, 53-56, 119, 122, and 123, which depend directly or indirectly from an allowable base claim, also are allowable. Applicant respectfully requests that this rejection be reconsidered and withdrawn.

The Lassner Reference

Claims 1-4, 6-15, 17-23, 30-40, 42-56, and 116-123 stand rejected over Lassner *et al.* (1995), *J. Reconstructive Microsurgery* 11(6):447-453 ("Lassner") under 35 U.S.C. §102(b). Claims 2-4 and 116 are cancelled without prejudice, rendering their rejection moot. Lassner investigated methods of preserving peripheral nerve grafts. The paragraph bridging columns 1 and 2 of page 448 of Lassner describes three experimental groups: nerve segments placed in cold storage at 4 °C under ischemic conditions for periods of 14 hours, 32 hours, 72 hours, or 120 hours (Groups A-H); normal animal controls having the nerve dissected, left in the animal, and subsequently sutured in the absence of extracorporeal pretreatment (Group K), and negative controls where nerves were subjected to repeated freezing and thawing to evacuate all viable cells (Group I). Therefore, the nerve sections were (1) removed from the animal and stored in cold, ischemic conditions prior to implantation, (2) left in the animal after nerve dissection and subsequently sutured, or (3) removed from the animal and rendered acellular prior to implantation.

These activities do not rise to the level of culturing. The cold, ischemic conditions are stasis conditions and do not promote physiological activity. In Applicant's system, if there is no physiological activity, there is no degradation of CSPGs and, thus, no enhancement of post-implantation axonal traversal of an interface between the nerve graft and host nerve tissue. Thus, Lassner's stasis conditions are not culturing conditions, and certainly they are not conditions permissive to CSPG degradation or enhancement of post-implantation axonal traversal of an interface between the nerve graft and host nerve tissue. Furthermore, leaving the severed nerve in the animal is not an *in vitro* treatment and, thus, is not relevant to the amended independent claims that involve culturing *in vitro*. In none of the three described dispositions of nerve

segments does Lassner disclose or even suggest degrading CSPG's by culturing a nerve graft *in vitro*.

In a second series of experiments, nerve grafts were prepared as described above, dissected into small segments, placed in a culture dish containing Dulbecco's Modified Eagle Medium, and maintained at 5% CO_2/95% air for two days. The tissue segments were then evaluated morphologically, fixed with methanol at -18 °C, and immunohistologically stained without any reimplantation. Thus, these experiments are merely histological in nature and not a method for preparing a nerve graft (claim 1) or a method for enhancing the regenerative potential of a nerve graft (claim 38). Additionally, the described conditions do not necessarily result in degradation of CSPGs or enhancement of post-implantation axonal traversal of an interface between the nerve graft and host nerve tissue. As explained above in connection with Dennis, it is improper to infer such activity from any particular set of conditions.

Accordingly, for the reasons provided above, amended independent claims 1 and 38 are novel over Lassner. Claims 6-15, 17-23, 30-40, 42-56, and 117-123 which depend directly or indirectly from an allowable base claim, also are allowable. Applicant respectfully requests that this rejection be reconsidered and withdrawn.

Rejection Under 35 U.S.C. §103(a)

Claims 1-4, 6-23, 30-40, 42-56, and 116-123 stand rejected over Dennis, La Fleur, Ide *et al.* (1983), Brain Research 288:61-75 ("Ide"), and Evans *et al.* (1994), Prog. Neurobiology, 43:187-233 ("Evans") under 35 U.S.C. §103(a). Claims 2-4 and 116 are cancelled without prejudice, rendering their rejection moot. As mentioned above, both Dennis and La Fleur fail to describe degrading chondroitin sulfate proteoglycan (CSPG) of a nerve graft comprising a nerve tissue segment and having an intact basal lamina tube by *in vitro* culturing, thereby enhancing post-implantation axonal traversal of an interface between the nerve graft and host nerve tissue relative to an untreated nerve graft. Neither Ide nor Evans cures the deficiency of Dennis or La Fleur as the former are directed to *in vivo* predegeneration. Evans additionally reports that predegeneration has no clinical relevance, teaching away from any combination. (Page 212.)

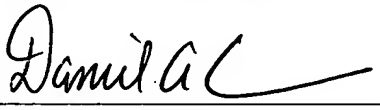
Accordingly, for the reasons provided above, amended independent claims 1 and 38 are patentable over Dennis, La Fleur, Ide, and/or Evans. Claims 6-23, 30-40, 42-56, and 117-123,

which depend directly or indirectly from an allowable base claim, also are allowable. Applicant respectfully requests that this rejection be reconsidered and withdrawn.

CONCLUSION

In view of the foregoing, Applicant respectfully requests that the foregoing rejections be reconsidered and withdrawn. The Examiner is invited to contact the undersigned attorney with any questions about this submission. Early favorable action is respectfully solicited.

Respectfully submitted,



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